Clin. Cardiol. 27, 3–8 (2004)

Review

Optimizing Adjunctive Antithrombotic Therapy in the Treatment of Acute Myocardial Infarction: A Role for Low-Molecular-Weight Heparin

David Brieger, MBBS, PH.D., FRACP

Department of Cardiology, University of Sydney, Sydney, and Department of Cardiology, Concord Hospital, Concord, New South Wales, Australia

Summary: Thrombotic complications account for a large proportion of in-hospital deaths from acute myocardial infarction (MI). Although thrombolytic therapy has greatly improved clinical outcomes following MI, thrombin released during clot lysis has a prothrombotic effect, and the thrombolytic agents themselves may directly activate platelets. Antithrombotic therapy as an adjunct to thrombolysis improves the speed and extent of artery recanalization and reduces the incidence of secondary ischemic complications. The current treatment standard is unfractionated heparin (UFH) administered intravenously for 24–48 h. However, UFH has not been unequivocally shown to improve outcomes in large-scale, randomized clinical trials, and shows no evidence of benefit when used as an adjunct to streptokinase-based thrombolysis. Unfractionated heparin also has several clinical and practical disadvantages, such as the need for coagulation monitoring, difficulties attaining a stable and reliable anticoagulant effect, and the risk of hemorrhagic side effects. Low-molecular-weight heparin (LMWH) represents a safe and effective alternative antithrombotic therapy, with a stable and predictable anticoagulant effect, potential for use in combination with either fibrin-specific or streptokinase-based thrombolysis, no need for anticoagulation monitoring, and a low risk of hemorrhagic and other heparin-related complications. Several randomized clinical trials have shown that adjunctive LMWH is at least as effective as UFH in the acute phase of MI, is associated with fewer in-hospital recurrent ischemic events, and has an acceptable safety profile.

Address for reprints:

David Brieger, Ph.D.
Department of Cardiology
Concord Hospital, Hospital Road
Concord, NSW 2139, Australia
e-mail: davidb@email.cs.nsw.gov.au

Received: November 8, 2002
Accepted: February 14, 2003

Key words: acute myocardial infarction, thrombolysis, antithrombotic therapy, unfractionated heparin, low-molecular-weight heparin, enoxaparin

Introduction

Despite advances in the early management of ST-segment elevation myocardial infarction (STEMI), mortality and morbidity in these patients remain high.[1] Although arrhythmic consequences of left ventricular dysfunction account for some of these events, a significant proportion are caused by thrombotic complications which result from an increase in thrombin activity after an infarction. Paradoxically, thrombolytic drugs, which are given to hasten dissolution of the culprit coronary occlusive thrombus, may themselves contribute to this augmented thrombin activity.

Although thrombolytic therapy has demonstrated unequivocal benefit in the treatment of STEMI,[2–7] these agents directly activate platelets.[8] In addition, clot lysis during thrombolytic therapy releases a pool of trapped, clot-bound thrombin, which is then available for continued thrombus propagation.[8] Clinical outcomes after thrombolysis are largely governed by the speed and extent of restoration of patency to the infarcted artery and the prevention of secondary ischemic complications, such as reinfarction due to secondary thrombosis.[9] Early management therefore involves a multifaceted approach comprising a thrombolytic, an antiplatelet, and an antithrombin agent.

Recent advances in thrombolytic therapy, such as bioengineered variants of the tissue plasminogen activator (reteplase, tenecteplase), which can be administered as bolus regimens, have simplified the management of STEMI, facilitated early treatment, and have been adopted rapidly into the standard of care. In contrast, there has been little change in the antithrombotic component of adjunctive therapy, and unfractionated heparin (UFH) is still the most widely used agent worldwide.[10] In this review, emerging data concerning the use of low-molecular-weight heparin (LMWH) as an alternative to UFH will be presented, highlighting the clinical and practical advantages of this newer therapy.

Antithrombotic Therapy in ST-Segment Elevation MI

Unfractionated Heparin

Current guidelines from the American College of Cardiology (ACC)/American Heart Association (AHA) and the Taskforce of the European Society of Cardiology for the management of patients with STEMI recommend that UFH be started concurrently with thrombolytic therapy and continued for at least 48 h.[11, 12] It is important to note that, despite the consistency of these recommendations, the underlying evidence for them comes only from small studies with angiographic endpoints that demonstrated improved outcomes with intravenous UFH.[13–16] There are no unequivocal data from large, randomized clinical trials confirming the benefits of UFH over placebo as adjunctive therapy to thrombolytic agents. In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI) 2 study and the Third International Study of Infarct Survival (ISIS-3), subcutaneous UFH plus tissue plasminogen activator (t-PA) conferred no mortality advantage over t-PA alone.[3, 17] In the Global Use of Strategies To open Occluded coronary arteries (GUSTO) trial, the best outcomes were observed in patients receiving accelerated t-PA plus intravenous UFH, but no patient group received the same regimen of t-PA alone,[5] therefore it is not possible to determine whether the benefit of accelerated t-PA was increased by, or independent of, concomitant UFH.

Neither the ISIS-3 nor the GISSI-2 study demonstrated improved outcomes using streptokinase plus subcutaneous UFH compared with streptokinase alone.[3, 17] Thus, there is no compelling evidence for the use of UFH in conjunction with streptokinase-based regimens.[11]

Unfractionated heparin has several practical disadvantages. Patients receiving intravenous UFH require frequent coagulation monitoring because of its unpredictable anticoagulant effect. Even with dose adjustment to maintain appropriate activated partial thromboplastin times (aPTTs), consistent levels of anticoagulation are difficult to achieve. In the GUSTO I and Thrombolysis in Myocardial Infarction (TIMI) 9B studies, approximately half the UFH-treated patients had aPTTs below the target level.[18, 19] This is particularly important, given that improved patency was closely tied to adequate anticoagulation in earlier angiographic studies of adjunctive UFH.[13, 14] Treatment with UFH also carries a significant risk of hemorrhagic complications, in view of which the ACC/AHA guidelines recommend weight-adjusted dosing.[12] The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen-3 (ASSENT-3) trial, which used the recommended weight-adjusted dose of UFH, reported fewer major bleeding complications and a lower rate of blood transfusions than the ASSENT-2 trial, which used a less fully weight-adjusted UFH dose.[20, 21] Other heparin-related side effects include heparin-induced thrombocytopenia, osteoporosis, and local heparin-related skin allergy.[22, 23]

Theoretical Advantages of LMWH

Following administration, LMWH is cleared by the reticuloendothelial system less avidly than UFH, and binds less strongly to circulating plasma proteins,[24, 25] resulting in a longer half-life and more stable levels of anticoagulation. Furthermore, LMWH results in greater inhibition of thrombin generation (higher anti-factor Xa:anti-factor IIa ratio) and prolonged anti-factor Xa activity (Table I). Additional advantages of LMWH over UFH include greater inhibition of von Willebrand factor and less platelet activation, resulting in a greater net antiplatelet effect than UFH.[24–26] Unlike UFH, patients receiving LMWH do not require coagulation monitoring.[24] In addition, LMWH is administered as convenient subcutaneous injections, either once or twice daily.

There is now considerable experience with several LMWHs in the management of acute coronary syndromes (ACS), in which a combined antiplatelet and anticoagulant regimen is also the recommended approach.[27] In ACS, the LMWH enoxaparin has consistently shown sustained improvements in ischemic outcomes compared with UFH[28–30] and is less likely than UFH to induce rebound ischemia.[31]

LMWH as an Adjunct to Streptokinase

Although large randomized clinical trials have failed to demonstrate any clinical benefits with subcutaneous UFH as an adjunct to streptokinase-based thrombolysis, LMWH has shown clinical potential in this setting (Table II).[32–35]

The randomized, double-blind, placebo-controlled Biochemical Markers in Acute Coronary Syndromes (BIOMACS II) trial evaluated dalteparin as an adjunct to streptokinase and aspirin in 101 patients with STEMI.[35] Dalteparin showed a nonsignificant trend toward higher rates of TIMI flow grade 3 in infarcted arteries (68% with dalteparin vs. 51% with placebo, $p = 0.10$), and a lower incidence of recurrent ischemia (16 vs. 38%, $p = 0.04$).

In the placebo-controlled Fragmin in Acute Myocardial Infarction (FRAMI) trial of dalteparin as an adjunct to streptokinase ($n = 776$), dalteparin significantly reduced the incidence of left ventricular thrombus formation in patients with acute anterior myocardial infarction.[33] Dalteparin was associated with higher bleeding rates than placebo (2.9 vs. 0.3%).

The placebo-controlled Acute Myocardial Infarction-Streptokinase (AMI-SK) study (496 patients) evaluated enoxaparin for 3–8 days in conjunction with streptokinase.[34] Enoxaparin therapy significantly improved arterial patency (70 vs. 58%, $p = 0.01$) and significantly reduced the incidence of the composite 30-day triple endpoint of death, reinfarction, and recurrent angina (13 vs. 21%, $p = 0.03$). These improvements in clinical outcomes were attained at the expense of a nonsignificant increase in the rate of major hemorrhage (4.8 vs. 2.5%, $p = 0.2$).

Recently, enoxaparin has been directly compared with UFH in 300 patients receiving thrombolytic therapy (mostly streptokinase). Antithrombin treatment was given for 4 days, and the primary combined endpoint (death, nonfatal reinfarction, or readmission for unstable angina) was assessed at 90 days.[32] Enoxaparin reduced the rate of the combined endpoint (26 vs. 36%, $p = 0.04$) without an excess in the rate of major hemorrhage (3 vs. 4% for enoxaparin and UFH, respectively). There was evidence to suggest that the incidence of rebound clinical events was re-

Table I The advantages and limitations of antithrombotic therapy with low-molecular-weight heparin compared with unfractionated heparin

	Advantage	Limitation
Pharmacologic	Higher anti-Xa:anti-IIa ratio	Antithrombotic effect cannot be "stopped" immediately, in case of emergency, e.g., immediate surgical intervention required
	High bioavialability (~90%) Longer half-life (2–4 times UFH) Prolonged anti-Xa activity Greater inhibition of von Willebrand factor (level differs between the LMWHs) Less platelet activation Resistance to inactivation by platelet factor 4	
Clinical	Effective with both streptokinase-based and fibrin-specific thrombolysis Less recurrent ischemia or infarction Fewer heparin-related side effects (e.g., HIT, local skin reactions) No need for coagulation monitoring	
Practical	Convenient once- or twice-daily injections Cost effective	More expensive

Abbreviations: HIT = heparin-induced thrombocytopenia, LMWH = low-molecular-weight heparin, UFH = unfractionated heparin.

Table II Summary of clinical trials of low-molecular-weight heparin as an adjunct to streptokinase-based thrombolysis

Trial	LMWH	Comparator Regimens	Patients (n)	Efficacy outcomes	Safety outcomes
BIOMACS II[35]	Dalteparin	Placebo	101	Rate of TIMI 3 flow: 68% with dalteparin vs. 51% with placebo p = 0.10) Rate of recurrent ischemic episodes at 6–24 h: 16% with dalteparin vs. 38% with placebo (p = 0.04)	No cerebral bleeds Incidence of hemorrhage higher in dalteparin group (5/6 events, 2 major bleeds)
FRAMI[33]	Dalteparin	Placebo	776 (517 evaluable)	Incidence of thrombus/embolism: 14.2% with dalteparin vs. 21.9% with placebo (p = 0.03)	Incidence of major hemorrhage: 2.9% with dalteparin vs. 0.3% with placebo (p = 0.006)
AMI-SK[34]	Enoxaparin	Placebo	496	Rate of TIMI 3 flow: 70% with enoxaparin vs. 58% with placebo (p = 0.01) Triple endpoint (death, reinfarction, and recurrent angina) at 0 days: 13% with enoxaparin vs. 21% with placebo (p = 0.03)	Incidence of major hemorrhage at 30 days: 4.8% with enoxaparin vs. 2.5% with placebo (p = 0.2)
Baird *et al.*[32]	Enoxaparin	UFH	300	Incidence of 90-day composite end-point (death, nonfatal reinfarction, or admission for UA): 36% with UFH vs. 26% with enoxaparin (p = 0.04)	Incidence of major hemorrhage: 4% with UFH vs. 3% with enoxaparin

Abbreviations: TIMI flow = Thrombolysis in Myocardial Infarction flow (grades 0–3), UA = unstable angina, BIOMACS = BIOchemical Markers in Acute Coronary Syndrome, FRAMI = FRagmin in Acute Myocardial Infarction, AMI-SK = Acute Myocardial Infarction-Streptokinase. Other abbreviations as in Table I.

duced by enoxaparin: the rate of reinfarction from Days 4–6 was 6.6% with UFH but only 2.2% with enoxaparin (p = 0.05).

In the smaller trials of LMWH with streptokinase, a reduction in the incidence of reinfarction and/or recurrent ischemia was consistently observed. Recently, the Hirulog and Early Reperfusion or Occlusion (HERO-2) study demonstrated that, in patients receiving streptokinase, the direct antithrombin agent bivalirudin reduced rates of reinfarction compared with UFH.[36]

However, this benefit was achieved with a significant financial cost and a small incremental risk of bleeding. The average cost of bivalirudin is currently more than US $400 per dose, therefore the combined cost of bivalirudin and streptokinase approaches that of the recombinant fibrinolytic drugs, thus removing the major incentive for the use of streptokinase.[37]

When compared with the direct thrombin inhibitors, the ease of use and modest cost of LMWH renders the latter more attractive in less affluent countries where streptokinase is the most widely used thrombolytic drug. Therefore, if the promising data from the phase 2 trials were to be confirmed in large-scale studies, the combination of streptokinase with LMWH could have global application and therefore a major impact on outcomes following ST-segment elevation myocardial infarction (STEMI).

LMWH as an Adjunct to Fibrin-Specific Thrombolysis

Table III summarizes the clinical experience to date with LMWH in combination with fibrin-specific thrombolytic agents. The feasibility of LMWH therapy was established in the small-scale Fraxiparin Anticoagulant Therapy in Myocardial Infarction Study Amsterdam (FATIMA) trial,[38] which monitored anti-factor Xa levels during therapy with t-PA and the LMWH nadroparin. From 12 h onward, 88% of all anti-factor Xa measurements fell within target range, obviating the need for coagulation monitoring. Arterial patency rates were high, and there were no major bleeding complications. Further support for LMWH in this setting has been provided by the ASSENT-PLUS trial.[39] Preliminary data indicate that dalteparin, as an adjunct to t-PA and aspirin, is associated with a trend toward increased arterial patency rates compared with UFH, with a similar incidence of bleeding complications in both groups (Table III). However, there were no differences between the groups in the incidence of clinical events (death, reinfarction, revascularization) at 30 days.

The Second Trial of Heparin and Aspirin Reperfusion Therapy (HART II), in which 400 patients receiving accelerated t-PA were randomized to UFH or enoxaparin, confirmed that enoxaparin is at least as effective as UFH. Patency rates at 90 min were 80.1% in the enoxaparin group and 75.1% in the UFH group.[40] Patients with patent arteries underwent a second angiogram at 5–7 days, and the

TABLE III Summary of clinical trials of low-molecular-weight heparin as an adjunct to fibrin-specific thrombolysis

Trial	LMWH	Comparator regimens	Patients (n)	Efficacy outcomes	Safety outcomes
FATIMA[38]	Nadroparin	None	30	TIMI 2 or 3 flow (patency) in 80% patients. Mean anti-Xa level: 0.52 U/ml 88% patients within target range after 12 h	No major bleeding complications (minor events in two patients)
ASSENT-PLUS[39]	Dalteparin	UFH	400	Full results not published. Preliminary report of trend with dalteparin toward increased rates of TIMI 3 flow, lower rates of TIMI 0 or 1 flow, and reduction in thrombus formation. Significant reduction with dalteparin in rate of recurrent MI	No differences in major or minor bleeding between the dalteparin and UFH groups
HART II[40]	Enoxaparin	UFH	400	Rates of TIMI 2 or 3 flow: 80.1% with enoxaparin vs. 75% with UFH. Reocclusion rates at 5–7 days higher with UFH	Rates of adverse event similar in enoxaparin and UFH groups
ENTIRE-TIMI 23[41]	Enoxaparin	UFH (Also half-dose TNK + abciximab + UFH/ enoxaparin. Results not shown)	483	Rates of TIMI 3 flow at 60 min: 48–51% with enoxaparin vs. 52% with UFH. Rates of death/ recurrent MI at 30 days: 4.4% with enoxaparin vs. 15.9% with UFH (p = 0.005)	Major hemorrhagic events (with full-dose TNK, no abciximab): 1.9% with enoxaparin vs. 2.4% with UFH
ASSENT-3[20]	Enoxaparin	UFH (Also half-dose TNK + abciximab + UFH. Results not shown)	6,095	Incidence of composite endpoint (death, in-hospital reinfarction, or refractory ischemia at 30 days): 11.4% with enoxaparin vs. 15.4% with UFH (p = 0.0002)	Major bleeding: 3.0% with enoxaparin vs. 2.2% with UFH (p = NS)

Abbreviations: NS = not significant, FATIMA = Fraxiparin Anticoagulant Therapy in Myocardial Infarction Study Amsterdam, ASSENT = ASsessment of the Safety and Efficacy of a New Thrombolytic regimen, HART = Heparin and Aspirin Reperfusion Therapy, TIMI = Thrombolysis in Myocardial Infarction. Other abbreviations as in Tables I and II.

rate of reocclusion was lower in the enoxaparin group than in the UFH group (5.9 vs. 9.8%). These benefits of enoxaparin were achieved without an increase in adverse events.

In the Enoxaparin and TNK-TPA with or without GP IIb/IIIa Inhibitor as REperfusion strategy in ST Elevation MI (ENTIRE-TIMI) 23 trial (n = 483), in which the thrombolytic regimen was full-dose tenecteplase, TIMI-3 flow rates at 60 min were similar in the UFH and enoxaparin groups (52 vs. 48–51%). It is important, however, that the rate of recurrent ischemic events at 30 days was 15.9% with UFH and 4.4% with enoxaparin (p = 0.005).[41] The large, randomized, open-label ASSENT-3 trial (n = 6,095) showed that, as an adjunct to tenecteplase, enoxaparin reduced the primary endpoint (a composite of mortality, in-hospital reinfarction, or in-hospital refractory ischemia at 30 days) compared with UFH: 11.4 vs. 15.4%, relative risk 0.74, confidence interval (CI) 0.63 to 0.87 (p = 0.0002).[20] This difference was driven by a reduction in in-hospital reinfarction and refractory ischemia in the enoxaparin group. Enoxaparin significantly reduced the incidence of the combined safety and efficacy endpoint compared with UFH: 13.7 vs. 17.0%, relative risk 0.81, CI 0.70 to 0.93 (p = 0.0037). The risk of major hemorrhagic complications was similar for UFH and enoxaparin (2.2 vs. 3.0% p = not significant). Despite the clinically useful data generated by the ASSENT-3 trial, it was not designed to test a prespecified hypothesis, and a larger confirmatory trial is planned, the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment (ExTRACT-TIMI 25) trial. In this study the thrombolytic agent will not be specified and 20,000 patients will be randomized to either UFH or LMWH.

Prehospital Fibrinolysis and LMWH

There is unequivocal evidence that the earlier reperfusion is initiated, the greater the benefit.[2] The mortality rate in enoxaparin-treated patients in the ASSENT-3 trial (5.4%) was among the lowest reported in a fibrinolytic trial, despite the median time-to-treatment (2.7 h) being similar to other studies. A protocol of bolus thrombolytic therapy followed by LMWH lends itself to prehospital thrombolysis, which may improve these results even further. This strategy has been investigated in the ASSENT-3 PLUS study by comparing patients treated with tenecteplase plus prehospital UFH or LMWH.[42] In this study, which enrolled 1,639 patients, treatment with LMWH tended to lower the frequency of in-hospital ischemic complications or death at 30 days (14.2 vs. 17.4% for UFH, p=0.080), although there was no difference for this composite endpoint plus in-hospital intracranial hemorrhage or major bleeding. The increased intracranial hemorrhage was seen exclusively in patients >75 years of age and has been attributed to the lower creatinine clearance in elderly patients. In the ExTRACT-TIMI 25 study, the enoxaparin dose has been reduced in patients over the age of 75.

Conclusions

Fibrinolytic therapy remains the most widespread form of reperfusion therapy for STEMI. Adjunctive therapy with LMWH offers significant practical advantages compared with UFH. Randomized clinical trials have shown that LMWH is at least as effective as UFH as an adjunct to both fibrin-specific and streptokinase-based thrombolytic regimens. Low-molecular-weight heparin also has more favorable effects on secondary ischemic events following STEMI, and the clinical benefits are achieved without an increase in major bleeding or thrombocytopenia. These clinical advantages, together with its convenience and modest cost, ensure that LMWH should evolve as the adjunctive antithrombotic agent of choice for patients with STEMI.

References

1. Kuch B, Bolte H-D, Hoermann A, Meisinger E, Loewel M: Regimen (ASSENT)-3 Investigators: Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab or unfractionated heparin: The ASSENT-3 randomised trial in acute myocardial infarction. *Lancet* 2001;358:605–613
2. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group: Indications for fibrinolytic therapy in suspected acute myocardial infarction: Collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 1994;343:311–322
3. ISIS-3 (Third International Study of Infarct Survival) Collaborative Group: ISIS-3: A randomised comparison of streptokinase vs. tissue plasminogen activator vs. anistreplase and of aspirin plus heparin vs. aspirin alone among 41,299 cases of suspected acute myocardial infarction. *Lancet* 1992;339:753–770
4. The International Study Group: In-hospital mortality and clinical course of 20,891 patients with suspected acute myocardial infarction randomised between alteplase and streptokinase with or without heparin. *Lancet* 1990;336:71–75
5. The GUSTO investigators: An international randomised trial comprising four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;329:673–682
6. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group: Randomised trial of intravenous streptokinase, oral aspirin, both or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;2:349–360
7. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI): Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986;1: 397–402
8. Seitz R, Pelzer H, Immel A, Egbring R: Prothrombin activation by thrombolytic agents. *Fibrinolysis* 1993;7:109–115
9. Ross AM, Coyne K, Hammond M, Lundergan CF: Low-molecular-weight heparins in acute myocardial infarction: Rationale and results of a pilot study. *Clin Cardiol* 2000;23:483–485
10. Klein W, Kraxner W, Hödl R, *et al*., for the GRACE Investigators: Improved survival and reduced bleeding across all ACS subsets: Findings from the Global Registry of Acute Coronary Events (GRACE). *J Am Coll Cardiol* 2002;39(suppl A):444A
11. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology: Acute myocardial infarction: Pre-hospital and in-hospital management. *Eur Heart J* 1996;17:43–63
12. Ryan TJ, Antman EM, Brooks NH, Califf RM, Hillis LD, Hiratzka LF, Rapaport E, Riegel B, Russell RO, Smith EE III, Weaver WD, Gibbons RJ, Alpert JS, Eagle KA, Gardner TJ, Garson A Jr, Gregoratos G, Ryan TJ, Smith SC Jr, for the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction): 1999 Update: ACC/AHA guidelines for the management of patients with acute myocardial infarction. *J Am Coll Cardiol* 1999;34:890–911
13. de Bono DP, Simoons ML, Tijssen J, Arnold AE, Betriu A, Burgersdijk C, Lopez Bescos L, Mueller E, Pfisterer M, Van de Werf F, Zijistra F, Verstraete M: Effect of early intravenous

heparin on coronary patency, infarct size, and bleeding complications after alteplase thrombolysis: Results of a randomised double-blind European Cooperative Study Group. *Br Heart J* 1992;67:122–128
14. Hsia J, Hamilton WP, Kleiman N, Roberts R, Chaitman BR, Ross AM: A comparison between heparin and low-dose aspirin as adjunctive therapy with tissue plasminogen activator for acute myocardial infarction. Heparin-Aspirin Reperfusion Trial (HART) Investigators. *N Engl J Med* 1990;323:1433–1437
15. Bleich SD, Nichols T, Schumacher R, Cooke DH, Tate DA, Teichman SL: Effect of heparin on coronary arterial patency after thrombolysis with tissue plasminogen activator in acute myocardial infarction. *Am J Cardiol* 1990;66:1412–1417
16. Prins MH, Hirsh J: Heparin as an adjunctive treatment after thrombolytic therapy for acute myocardial infarction. *Am J Cardiol* 1991;67:3A–11A
17. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico: GISSI-2: A factorial randomised trial of alteplase versus streptokinase and heparin versus no heparin among 12,490patients with acute myocardial infarction. *Lancet* 1990;336:65–71
18. Granger CB, Hirsch J, Califf RM, Col J, White HD, Betriu A, Woodlief LH, Lee KL, Bovill EG, Simes RJ, Topol EJ: Activated thromboplastin time and outcome after thrombolytic therapy for acute myocardial infarction. Results from the GUSTO-I trial. *Circulation* 1996;93:870–878
19. Antman EM: Hirudin in acute myocardial infarction. Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9B trial. *Circulation* 1996;94:911–921
20. The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators: Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab or unfractionated heparin: The ASSENT-3 randomised trial in acute myocardial infarction. *Lancet* 2001;358:605–613
21. Assessment of the Safety and Efficacy of a New Thrombolytic Investigators: Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: The ASSENT-2 double-blind randomised trial. *Lancet* 1999;354:716–722
22. Nelson-Piercy C: Hazards of heparin: Allergy, heparin-induced thrombocytopenia and osteoporosis. *Ballieres Clin Obstet Gynaecol* 1997;11:489%nd509
23. Warkentin TE, Levine MN, Hirsh J, Horsewood P, Roberts RS, Gent M, Kelton JG: Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionatedheparin. *N Engl J Med* 1995;332:1330–1335
24. Antman EM: The search for replacements for unfractionated heparin. *Circulation* 2001;103:2310–2314
25. Hirsh J, Warkentin TE, Shaughnessy SG, Anand SS, Halperin JL, Raschke R, Granger C, Ohman EM, Dalen JE: Heparin and low-molecular-weight heparin: Mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest* 2001;119(1 suppl):64S–94S
26. Brieger D, Dawes J: Characterisation of persistent anti-Xa activity following administration of the low molecular weight heparin enoxaparinsodium(Clexane). *ThrombHaemost* 1994;72:275–280
27. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, Jones RH, Kereiakes D, Kupersmith J, Levin TN, Pepine CJ, Schaeffer JW, Smith EE III, Steward DE, Théroux P, Alpert JS, Eagle KA, Faxon DP, Fuster V, Gardner TJ, Gregoratos G, Russell RO, Smith SC Jr: ACC/AHA Guideline update for the management of patients with unstable angina and non-ST segment elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). *J Am Coll Cardiol* 2000;36:970–1062
28. Cohen M, Demers C, Gurfinkel EP, Turpie AG, Fromell GJ, Goodman S, Langer A, Califf RM, Fox KA, Premmereur J, Bigonzi F: A comparison of low molecular weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q wave Coronary Events Study Group. *N Engl J Med* 1997;337:447–452
29. Antman EM, McCabe CH, Gurfinkel EP, Turpie AG, Bernink PJ, Salein D, Bayes De Luna A, Fox K, Lablanche JM, Radley D, Premmereur J, Braunwald E: Enoxaparin prevents death and cardiac ischaemic events in unstable angina/non-Q-wave myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI) 11B trial. *Circulation* 1999;100:1593–1601
30. Antman EM, Cohen M, Radley D, McCabe C, Rush J, Premmereur J, Braunwald E: Assessment of the treatment effect of enoxaparin for unstable angina/non-Q wave myocardial infarction. TIMI 11B-ESSENCE meta-analysis. *Circulation* 1999;100:1602–1608
31. Goodman SG, Barr A, Sobtchouck A, Cohen M, Fromell GJ, Laperriere L, Hill C, Langer A: Low molecular weight heparin decreases rebound ischemia in unstable angina or non-Q-wave myocardial infarction: The Canadian ESSENCE ST segment monitoring substudy. *J Am Coll Cardiol* 2000;36:1507–1513
32. Baird SH, Menown IB, Mcbride SJ, Trouton TG, Wilson C: Randomised comparison of enoxaparin with unfractionated heparin in patients receiving fibrinolytic therapy for acute myocardial infarction. *Eur Heart J* 2002;23:627–632
33. Kontny F, Dale J, Abildgaard U, Pedersen TR: Randomized trial of low molecular weight heparin (dalteparin) in prevention of left ventricular thrombus formation and arterial embolism after acute anterior myocardial infarction: The FRagmin in Acute Myocardial Infarction (FRAMI) study. *J Am Coll Cardiol* 1997;30:962–969
34. Simoons ML, Krzeminska-Pakula M, Alonso A, Goodman S, Kali A, Loos U, Gosset F, Louer V, Bigonzi F: Improved reperfusion and clinical outcome with enoxaparin as an adjunct to streptokinase thrombolysis in acute myocardial infarction. The AMI-SK study. *Eur Heart J* 2002;23:1282–1288
35. Frostfeldt G, Ahlberg G, Gustafsson G, Helmius G, Lindahl B, Nygren A, Siegbahn A, Swahn E, Venge P, Wallentin L: Low molecular weight heparin (dalteparin) as adjuvant treatment to thrombolysis in acute myocardial infarction—a pilot study: BIOchemical Markers in Acute Coronary Syndromes (BIOMACS II). *J Am Coll Cardiol* 1999;33:627–633
36. White H: Thrombin-specific anticoagulation with bivalirudin versus heparin in patients receiving figrinolkytic therapy for acute myocardial infarction: The HERO-2 randomised trial. La ncet 2001;358:1855–1863
37. *Drug Topics® RedBook® Update*, p. 345–346. Montvale, NJ: Medical Economics Company Inc., 2001
38. Chamuleau SA, de Winter RJ, Levi M, Adams R, Buller HR, Prins MH, Lie KJ, Peters RJ: LMWH as an adjunct to thrombolysis for acute myocardial infarction: The FATIMA study. Fraxiparin Anticoagulant Therapy in Myocardial Infarction Study Amsterdam (FATIMA) Study Group. *Heart J*998;80:35–39
39. Wallentin L, Dellborg M, Lindahl B, Nilsson T, Pehrsson K, Swahn E: The low-molecular-weight heparin dalteparin as adjuvant therapy in acute myocardial infarction: The ASSENT PLUS study. *Clin Cardiol* 2001;24(suppl 3):I12–I14
40. Ross AM, Molhoek P, Lundergan C, Knudtson M, Draoui Y, Regalado L, Le Louer V, Bigonzi F, Schwartz W, de Jong E, Coyne K: Randomized comparison of enoxaparin, a low molecular weight heparin, with unfractionated heparin adjunctive to recombinant tissue plasminogen activator thrombolysis and aspirin: Second trial of Heparin and Aspirin Reperfusion Therapy (HART II). *Circulation* 2001;104:648–652
41. Antman EM, Louwerenburg HW, Baars HF, Wesdorp JC, Hamer B, Bassand JP, Bigonzi F, Pisapia G, Gibson CM, Heidbuchel H, Braunwald E, Van de Werf F: Enoxaparin as adjunctive antithrombin therapy for ST-elevation myocardial infarction. Results of the ENTIRE-Thrombolysis in Myocardial Infarction (TIMI) 23 trial. *Circulation* 2002;105:1642–1649
42. Wallenrin L, Goldstein P, Armstrong PW, Granger CB, Adgey AA, Arntz HR, Bogaerts K, Danays T, Lindahl B, Makijarvi M, Verheugt F, Van de Werf F: Efficacy and safety of tenecteplase in combination with the low-molecular-weight heparin enoxaparin or unfractionated heparin in the prehospital setting: The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 PLUS randomized trial in acute myocardial infarction. *Circulation* 2003;108(2):135–142